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LETTER FROM MILES INC TO USEPA SUBMITTING A SUMMARY ON AN EVALUATION IN THE MOUSE MICRONUCLEUS TEST WITH TOLUENE DIISOCYANATE WITH ATTACHMENTS		
Chemical Category		
TOLUENE DIISOCYANATE (26471-62-5)		

"Contains NO CBI"

MILES

Miles Inc.
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December 21, 1992

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Office of Toxic Substances Room L-100
Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Attention: 8(d) Health and Safety Reporting F
(Notification/Reporting)

Gentlemen:

Enclosed is a copy of a Health and Safety Study Summary we have just received. We are submitting this study on behalf of Miles Inc., Mobay Road, Pittsburgh, Pennsylvania 15205. We are filing this Health and Safety Study to comply with the regulations codified at 40 CFR, Part 716. This submission contains no Confidential Business Information (CBI). A final report will be filed when it is received.

The information required is given below.

Chemical Name: Toluene diisocyanate (TDI)
CAS No: 26471-62-5
Name of Study: Toluene Diisocyanate: An Evaluation in the Mouse Micronucleus Test (Summary)

Submitting Official: Francis J. Rattay
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If you have any questions, please contact me.

Sincerely,

Francis J. Rattay
Manager, Regulatory Affairs
(412) 777-7471

Attachment
Certified Mail No.: P 827 215 582

TOLUENE DI-ISOCYANATE:
AN EVALUATION IN THE MOUSE MICRONUCLEUS TEST

SUMMARY

Toluene di-isocyanate (TDI) has been evaluated for its ability to induce micronucleated polychromatic erythrocytes in the bone marrow of C57BL/6JfCD-1/Alpk mice. Groups of 5 male mice were exposed to TDI for a 6 hour period by the inhalation route at target concentrations of 11.8 and 18.9ppm. Groups of 5 female mice were similarly exposed to TDI at target concentrations of 7.5 and 11.9ppm. In both cases these concentrations were selected to represent 50 and 80% respectively of a median lethal concentration (MLC) estimated in that sex over a four day observation period. Due to an error in the original calculation of the MLC values the target concentrations used actually represented approximately 62 and 99% of the MLC in males and 53 and 84% of the MLC in females. Bone marrow samples were taken 24 hours after the end of the exposure period for the lower concentrations and 24, 48 and 72 hours after the end of the exposure period for the higher concentrations.

Small but statistically significant increases in the incidence of micronucleated polychromatic erythrocytes, over the air control values, were observed in females 24 hours after being exposed at the target concentrations of 7.5ppm and 24 and 48 hours after being exposed at the target concentration of 11.9ppm. These increases were small and not concentration-related. Extended analysis of a further 2000 polychromatic erythrocytes from these animals and the female air control animals at the 24 and 48 hour time points was conducted. No statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes were observed in these extended counts. However, when the original and extended analyses were combined prior to statistical analysis small but statistically significant increases were observed in females 24 hours after being exposed at both target concentrations.

TOLUENE DI-ISOCYANATE:
AN EVALUATION IN THE MOUSE MICRONUCLEUS TEST

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SUMMARY - continued

Small but statistically significant increases in the incidence of micronucleated polychromatic erythrocytes, over the air control values, were observed in males 24 hours after being exposed at the target concentrations of 11.8 and 18.9ppm but there was no clear concentration-response relationship. Extended analysis of a further 2000 polychromatic erythrocytes from these animals and the male air control animals at the 24 hour time point was conducted. A small but statistically significant increase in the incidence of micronucleated polychromatic erythrocytes was observed only at the lower target concentration (11.8ppm) in these extended counts and when the original and extended analyses were pooled prior to statistical analysis.

In order to further investigate the increases observed in both males and females exposed to TDI and the lack of concentration-response relationships observed a second assay was conducted. Groups of 5 male mice were exposed to TDI for a 6 hour period by the inhalation route at target concentrations of 5.9, 11.8 and 18.9ppm and groups of 5 female mice were similarly exposed to TDI at target concentrations of 3.7, 7.5 and 11.9ppm. In both cases these concentrations were selected to represent the concentrations used in the first study with an additional lower concentration to investigate any concentration-response relationships. Due to the error in the original calculation of the MLC values, the target concentrations used actually represented approximately 31, 62 and 99% of the MLC in males and 26, 53 and 84% of the MLC in females. Bone marrow samples were taken 24 hours after the end of the exposure period for all concentrations.

In this second study high levels of lethality were observed at the 11.8ppm (62% MLC) concentration in males and the 11.9ppm (84% MLC) concentration in females and therefore the slides from the males exposed at the 5.9ppm

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SUMMARY - continued

target concentration and the females exposed at the 3.7 and 7.5ppm target concentrations only were analysed. The maximum concentration in each case is considered to represent a maximum tolerated concentration (MTC) in this second study.

No statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes, compared to the air control values, were observed in the males exposed to TDI.

Small but statistically significant increases in the incidence of micronucleated polychromatic erythrocytes, over the air control values, were observed in females 24 hours after being exposed at both the 3.7 and 7.5ppm target concentrations. These increases were small and the values fell within the range of female air control values reported in this study. It is therefore considered that the increases observed in this second study are due to a low control value rather than to any effect of TDI. The increases are therefore considered not to be biologically significant.

In summary, although increases in the incidence of micronucleated polychromatic erythrocytes were observed in both males and females exposed to TDI these increases were small, not concentration-related and were not reproducible at concentrations limited by lethality in a repeat study. It is therefore considered that the increases observed are of no biological significance and do not indicate any clastogenic activity of TDI in the mouse bone marrow micronucleus assay.

Consideration of the percentage of polychromatic erythrocytes showed statistically significant decreases, compared to the air control values, in both males and females in the first study and in females in the second

study. These decreases may indicate that TDI or a metabolite has induced a cytotoxic response in the bone marrow resulting in a depression of cell proliferation.

The test system positive control, vinyl chloride, induced statistically significant and biologically meaningful increases in micronucleated polychromatic erythrocytes, compared to the air control values, in both studies thus demonstrating the sensitivity of the test system to a known clastogen.

It is therefore concluded that TDI, under the conditions of test, is not clastogenic in the mouse micronucleus test.

CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

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